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The Treatment of Inoperable Sarcoma by
Bacterial Toxins (the Mixed Toxins of
the Streptococcus erysipelas and the
Bacillus prodigiosus)

BY

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The Treatment of Inoperable Sarcoma by Bacterial Toxins
(the Mixed Toxins of the *Streptococcus erysipelas* and
the *Bacillus prodigiosus*).

By WILLIAM B. COLEY, M.D. (New York.)¹

THE subject upon which I have been asked to address you is one upon which I have been working constantly the last seventeen years, and one which has grown more interesting to me with each succeeding year. While the results have not been as satisfactory as one who is seeking perfection could wish, they have been sufficiently real and tangible, I think, to be entitled to more careful consideration than they have yet received. Furthermore, they may have an important bearing upon the whole cancer problem, since, if by the administration of certain bacterial toxins we can cause the degeneration, death, and absorption of living tumour cells of one variety of cancer—sarcoma—it is not unreasonable to suppose that by the use of some other forms of bacterial toxins we may succeed in destroying or inhibiting the growth of the other and more common variety—carcinoma.

At the outset I wish, at the risk of tiring the few of you who may have read and remember some of my former papers upon this subject, to give in the briefest possible words an outline of the early history of the method of treatment, and the several stages of its development, for the benefit of the many who have never heard of the mixed toxins of

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erysipelas and *Bacillus prodigiosus*, or whose knowledge of the same is of the most general sort. Such early history of the method is essential for the proper consideration and understanding of its present status.

First, I wish to emphasize the point that the method rests upon a solid foundation of accepted and indisputable clinical facts—namely, that in a considerable number of cases of inoperable cancer of all varieties, and especially sarcoma, such tumours have been known entirely to disappear under attacks of accidental erysipelas, and patients have remained well for many years thereafter.

For those who refuse to accept clinical results unless confirmed by laboratory experiments, these latter tests have now been supplied, since during the last two years Dr. Martha Tracy and Dr. S. P. Beebe, of the Huntington Cancer Research Fund, have shown that large multiple sarcomas in dogs rapidly disappear under both local and systemic injections with the mixed toxins of erysipelas and *Bacillus prodigiosus*.

My attention was first called to the curative effect of accidental erysipelas in inoperable sarcoma by a certain case observed in 1891. In my studies of sarcoma at that time I made a careful analysis of all the cases of sarcoma (90 in number) operated upon at the New York Hospital during the preceding fifteen years. Among these cases was a small round-celled sarcoma of the neck, four times recurrent. At the fifth operation, in 1884, Dr. Bull found the tumour to involve the deep structures so extensively that it was impossible to remove it, and he gave up the attempt. The case was regarded as absolutely hopeless, when, shortly after the operation, the man developed a very severe attack of accidental erysipelas in the face and neck, followed two weeks later by a second attack. Within a few days after the beginning of the first attack the tumour began to soften and decrease rapidly in size. The history stated that when the patient left the hospital his tumours had entirely disappeared. There was no after-record of the case, but I made an effort to trace the patient, and finally found him alive and well, with no evidence of any local or general recurrence in the spring of 1891, seven years later. He was examined both by Dr. Bull and myself. (Fig. 1.)

At this time I had not read of Fehleisen's experiments in Germany in inoculating patients with inoperable malignant tumours with the streptococcus of erysipelas; but I was so strongly impressed with the case I have related that I determined to try inoculations in the first suitable case. In a very short time—May 2, 1891—I made my first

inoculation in a case of recurrent spindle-celled sarcoma of the tonsil and neck, kindly referred to me by Dr. William T. Bull. The patient was an Italian, aged 35, first operated upon for sarcoma of the tonsil and neck by Professor Durante, of Rome, in 1890, and again by Dr. William T. Bull, at the New York Hospital, in April, 1901. The tumour was found much too extensive for removal, but a portion was excised for microscopical examination, which proved it to be a spindle-celled sarcoma. At the time of my first inoculation there was a tumour



FIG. 1.

Recurrent round-celled sarcoma. Spontaneous recovery following accidental erysipelas. Photograph taken seven years after the cure.

of the right tonsil, nearly as large as an egg and almost completely blocking the pharynx; there was also a large metastatic tumour in the right cervical region. The patient could take no solid and little liquid food, and was much emaciated and cachectic. The details of this case were published in my first paper, "A Contribution to the Knowledge of Sarcoma."¹ The history of the case in brief is as follows: I worked

¹ *Ann. of Surg.* St. Louis, 1891, xiv, p. 199; and also *Amer. Journ. Med. Sci.*, Philad., 1893, cv, p. 487.

continuously from May to October, 1891, to produce an attack of erysipelas, without success. Cultures from four different laboratories were used and various methods of inoculation employed. Finally, in October, 1891, with 5 decigrams of a bouillon culture of streptococcus of erysipelas, just brought me from Koch's laboratory in Germany by Dr. Frank Ferguson, the pathologist of the New York Hospital, a most severe attack of erysipelas developed, nearly causing the death of the patient. Within an hour after the injection a severe chill occurred, followed by a temperature of 105° F. After an interval of twelve hours a typical attack of erysipelas developed, starting at the point of injection and extending over the neck and face. It ran its usual course. The tumour of the neck began to break down on the second day, and a discharge of broken-down tumour tissue continued until the end of the attack. At the end of two weeks the neck tumour had disappeared and the tonsil tumour had decreased in size. The patient remained well for eight years, and then died in Italy of a local recurrence.

During the next two years, through the kindness of Dr. Bull, I had an opportunity of trying the inoculations upon a number of chronic and incurable cases of malignant disease at the New York Hospital, in a special building erected for the purpose by Mr. Archer M. Huntington. It is necessary to refer to these earlier investigations with the inoculations of the living cultures, inasmuch as they form the basis of all the later work with the toxins.

Of the first ten cases treated by the living cultures (local and systemic injections of bouillon cultures of the streptococcus of erysipelas) six were sarcoma and four carcinoma, all inoperable and far advanced. In seven of the ten cases I could not produce erysipelas after many attempts extending over many weeks. In all these cases of failure to produce erysipelas, however, I noticed slight temporary improvement in the tumours as shown by decrease in size, increase in mobility, and diminution of vascularity. In only three cases of sarcoma was it possible to produce an active attack of erysipelas; one of these I have already related in brief. The second was a large inoperable sarcoma of the back (mixed-celled) with extensive metastases in the right groin of a man, aged 46. The tumour of the groin was partially removed, but recurred quickly. Specimens from the primary tumour of the back were excised and pronounced mixed-celled sarcoma by Dr. Frank Ferguson, pathologist to the New York Hospital, and the diagnosis was confirmed by microscopical examinations made by a number of other pathologists. I first

inoculated him on April 21, 1892. Injections with the living bouillon cultures of the streptococcus of erysipelas obtained from the laboratory of the College of Physicians and Surgeons were repeated daily for three weeks without causing an attack. In the fourth week an injection of 20 mm. of a fresh culture obtained from the Johns Hopkins Hospital Laboratory was given without effect. A second injection, two days later, was followed by a severe chill and a temperature of 105.5° F. Twenty-four hours later a typical area of erysipelas developed. To quote from my paper (loc. cit. 1893): "From the beginning of the attack the change that took place in the tumour was nothing short of marvellous. It lost its lustre and colour and had sunk visibly in size within twenty-four hours. Several sinuses formed the second day and discharged necrosed tumour-tissue. A few days later the tumour of the groin, which was about the size of a goose egg and very hard when the inoculations were begun, broke down and discharged a large amount of tumour-tissue. Three weeks from the date of the attack of erysipelas both tumours had entirely disappeared. July 1, two months later, there was a small local recurrence in the back. Two weeks later six small nodules had developed. Inoculations were resumed, but no attack of erysipelas could be produced until November 14, 1892, although constant attempts were made. By October 1 the tumour had been 2½ in. by 4½ in., and by November 14 5 in. by 3½ in., and there was a marked recurrence in the groin. On November 14, after an injection of 22 mm. of a culture previously used without effect, a moderately severe attack of erysipelas developed, during the course of which the tumours both in the back and groin disappeared. In two weeks there was evidence of recurrence. Curiously, during the next three months, three further attacks of erysipelas developed spontaneously; they were milder in character, and the effect upon the tumours was less pronounced and less lasting." Finally, early in 1893, under repeated injections of the mixed toxins of erysipelas and *Bacillus prodigiosus*, the tumour disappeared and the patient remained well for three and a quarter years, when he died of a malignant tumour of the abdomen, probably metastatic.

The third case of sarcoma in which I produced an attack of erysipelas was a twice-recurrent sarcoma of the breast in a woman aged 38, referred to me by Dr. Bull. An inoculation given June 2, 1892, resulted in a moderately severe attack of erysipelas. All of the three tumours present decreased considerably in size; one almost disappeared. A second attack of erysipelas was produced on June 30; the tumours showed some further improvement, but less than from the first attack. The check in

growth proved but temporary, and the tumours soon began to increase in size. In spite of further inoculations the patient grew worse and died within six months.

In none of the cases of carcinoma did I succeed in producing erysipelas. Although up to this time I had had no death, the difficulties in the way of successful inoculations were very great. Shortly afterward I had two deaths, both in far-advanced cases, and the patients had been duly warned of the risks of inoculation. These experiments with the living cultures, while absolutely confirming the curative influence of accidental erysipelas, as shown by clinical observation, also emphasized the practical difficulties which had been sufficient to cause Fehleisen to abandon his attempts. I had learned from the same source:—

(1) That it is extremely difficult to produce erysipelas at will ;

(2) That the risks of inoculation, when successful, were considerable ;

(3) And, most important, I had been impressed with the fact that repeated injections of the living bouillon cultures of the streptococcus of erysipelas had an inhibitory action upon the growth of the tumours which, while only temporary, was nevertheless distinct.

This fact led me to believe that a portion at least of the curative action of the erysipelas lay in the toxic products of the erysipelas, which might possibly be utilized without producing an actual attack of erysipelas.

In the latter part of 1892 I made my first experiments with the toxins of erysipelas. I began with bouillon cultures of the streptococcus of erysipelas, sterilized by just sufficient heat (58° C.) to destroy the germs, and also by filtering the unheated cultures through a porcelain filter. These toxins were prepared for me by Dr. Alexander Lambert. Four cases of inoperable sarcoma were treated by this preparation with constitutional reactions very similar to those obtained from the living cultures. The temperature would rise to 103·5° F., but would always fall to normal on the following day. There was some inhibitory action on the tumours, but this was temporary. I obtained cultures from fatal cases of erysipelas, in order to get the highest degree of virulence.

At this time, Roger's experiments with the prodigious cultures showed that if the *Bacillus prodigiosus* were grown together with the streptococcus of erysipelas the virulence of the latter was materially increased. Roger had never used the *Bacillus prodigiosus* alone or with the streptococcus of erysipelas on the human being, and had never, as far as I know, suggested it as a therapeutic agent.

In order to intensify the virulence of the erysipelas, I decided to use

the combined toxins of erysipelas and *Bacillus prodigiosus*, growing the two organisms together and sterilizing them with heat. The first preparation was made for me by Dr. B. H. Buxton, then Fellow of Bacteriology of the Loomis Laboratory, and now for seven years Professor of Experimental Pathology of Cornell University. The erysipelas culture was grown alone in bouillon for ten days, then the *Bacillus prodigiosus* added, the two grown together for ten days, and then sterilized by heating to 58° C., and kept sterile by the addition of a little thymol. This is the preparation that was used with little change until three years ago, when Dr. Martha Tracy, working with Dr. Buxton, suggested an important modification. Her subsequent experiments proved the truth of the opinion that I had already expressed some time before, based upon clinical observations alone—that the *Bacillus prodigiosus* had in itself a curative effect upon tumours, independent of any action it might have in intensifying the virulence of the erysipelas.

Tracy's first experiments with the *Bacillus prodigiosus* alone confirmed the investigations of Vaughan, of Ann Arbor—that the *Bacillus prodigiosus* toxins were the most powerful known. Further experiments with sarcoma in dogs showed that sarcoma would disappear under the injections with the prodigiosus alone, without any erysipelas, although not quite so rapidly as when the combined toxins were used. Utilizing these newly proven facts, Dr. Tracy proceeded to grow the two organisms separately and, by adding a certain definite quantity of the sterilized prodigiosus bouillon to each ounce of the streptococcus broth, was able to secure what had never been possible before—namely, a definite standardization of dosage. This enabled us to overcome the greatest difficulty we had had to contend with all along.

In the old way of growing the two organisms together, there had always been a varying amount of prodigiosus toxins in the solution, due to an exceedingly variable rate of growth. I had previously noted clinically that the highly coloured solution of the toxins, showing a large amount of prodigiosus present, were more powerful and, likewise, the curative effect was greater. The first preparations which Dr. Tracy made in the way described had so large an amount of prodigiosus that very severe reactions were obtained by minute doses, and in one case, in the hands of another physician, death resulted within a few hours after an injection of $\frac{1}{4}$ mm. made into a very vascular tumour in the mediastinal region. After this the addition of the prodigiosus to the toxins was immediately reduced to one half, and this amount has been continued up to the present time.

The process of preparation is as follows:—

To Prepare the Streptococcus Broth.—Soak 1 lb. minced beef overnight in 1,000 cc. of cold water. Then boil for one hour and filter through coarse cotton cloth of any sort. Add of peptone (Witte's) 10 gm.; of NaCl (sodium chloride) 5 gm. Test the reaction to litmus and render slightly alkaline by addition of a sufficient quantity of 10 per cent. NaOH (sodium hydroxide) solution. Boil for one hour. Filter through filter paper. Distribute into small flasks, 25 to 50 cc. in each flask. Sterilize by boiling for one half-hour on three successive days. Sow each flask with a few cc. of a broth culture of streptococcus.¹ Allow to grow in the incubator for three weeks.

To Prepare the Prodigiosus Suspension.—Spread an ordinary 2 per cent. agar medium to a depth of about 1 cm. at the bottom of a large "Roux" or "antitoxin" culture flask. Sterilize as usual by boiling for one half hour on three successive days. Over the surface of the agar, with the usual precautions against contamination, pour a two-day-old broth culture of *Bacillus prodigiosus*.² Manipulate the flask so that the entire agar surface has been touched by the broth, and drain off the surplus fluid. Allow the prodigiosus to grow at room temperature in daylight, but protected from the direct sunlight, for ten days. Scrape off the thick red growth with glass rods and rub up with a pestle and mortar to a smooth, rather thick suspension, using physiological salt solution as diluent. Bottle and sterilize in the bottle, by heat, at 75° C., for one hour. This suspension can be diluted further at any time. The amount of diluent needed is ascertained by determining the weight of nitrogen per cubic centimetre of suspension (Kjeldahl's method). This multiplied by 6.25 gives the weight of proteid present, and this should be 12.5 mgm. per cubic centimetre of the suspension to be used for the mixture.

To Prepare the Mixture.—Take of streptococcus broth culture, three weeks' growth, 100 cc.; of prodigiosus suspension (containing 12.5 mg. of proteid per cubic centimetre or 375 mg.³ of proteid in all) 30 cc.; of glycerine, 20 cc.

¹ The streptococcus used during the past two years in the laboratory of the Huntington Cancer Research Fund was isolated from a fatal case of septicæmia. It is doubtful whether an organism from an actual case of erysipelas would give any better results. The stock culture of streptococcus has been maintained more satisfactorily in broth than on agar. No attempt has been made in recent work to keep up the virulence by passing through animals.

² The stock culture of prodigiosus is kept upon agar slants, a tube of broth being inoculated from the agar two days before it is needed for the large flasks.

³ It was found desirable to reduce the amount of prodigiosus proteid to one-half of the amount shown in the formula given in my paper published in the *Medical Record*, New York, 1907, lxxi, p. 436.

Each cubic centimetre of the mixture then contains 2.5 mg. of prodigiosus proteid.

After mixing, bottle in glass-stoppered bottles. Add a small piece of thymol (size of pea to 1 oz. bottle) to each bottle, and sterilize two hours at 75° C. Keep on ice.

First, a further word upon the clinical observations of accidental erysipelas in inoperable tumours. In one of my earlier papers, "The Treatment of Malignant Tumours by Repeated Inoculation of the Living Germ of Erysipelas," I collected thirty-eight cases of malignant tumours (sarcoma and carcinoma) in which an attack of erysipelas had occurred, either by accident or by inoculation. In twenty-three cases the attack was accidental, and in fifteen the result of inoculation. Seventeen were sarcoma, seventeen carcinoma, and in four cases the type of tumour was not stated. Of the seventeen cases of carcinoma, three were permanently cured. One, a probable carcinoma, was well five years after the attack of erysipelas. The remaining thirteen showed more or less temporary improvement. Of the seventeen cases of sarcoma, seven were well from one to seven years afterwards. In the remaining ten cases, nearly all showed improvement, some disappearing entirely and later recurring.

In the *American Journal of Medical Sciences*, 1906, I published six other cases of cancer—five epithelioma, and one sarcoma—in which an attack of erysipelas had intervened in the course of the disease:—

- (1) Recurrent cancer of the breast. Patient well nine years.
- (2) Sarcoma of the neck (entire disappearance). Patient well eight years.
- (3) Epithelioma of the face, eighteen years' duration (entire disappearance). Local recurrence several years later. Again disappeared under one month's treatment with the toxins. Probable recurrence six months later.
- (4) Epithelioma of the face, lip, and nose. Disappeared under very severe attack of erysipelas. Patient well two years later, when he died of another trouble.
- (5) Epithelioma of the face of two years' duration. Entire disappearance under attack of erysipelas. Patient well at last observation, six months later.
- (6) Epithelioma of nose. Eight years' duration. Entire disappearance under attack of erysipelas. Patient well several years later.

THE ACTION OF THE MIXED TOXINS UPON INOPERABLE SARCOMA.

The macroscopic as well as the microscopic changes observed by myself and others have been precisely the same as those formerly noted in cases of sarcoma treated by inoculation of the living germ. First,

the tumour becomes much paler owing to decreased vascularity; second, it becomes much more movable and less fixed to the surrounding tissues, these changes being often noted after the first two or three injections; third, it soon begins to show areas of softening, due to caseous degeneration or necrobiosis of the tumour elements; fourth, gradual disappearance, either by absorption—which is more apt to be the case in the firmer tumours (*e.g.*, spindle-cell or fibro-sarcomas)—or, in other cases (especially the round-celled and vascular varieties), by breaking down and liquefaction of the tumour-tissues. In such cases incision and drainage may be sometimes advisable, provided the tumours are in accessible regions.

These changes are precisely the same, whether the toxins have been injected directly into the tumour or whether the injections have been made in remote parts of the body, proving that the action of the toxins is systemic rather than local. In a certain number of cases—in my own experience in a little over 10 per cent.—the degenerative progress has gone on until complete absorption of the tumours has taken place and the patients have remained cured. In other cases improvement is only temporary, and after a few weeks, in spite of continued injections and increased doses, the tumour again begins to show signs of growth and continues until a fatal issue. In a very few instances, especially in cases of very large and vascular tumours, particularly the melanotic type—which of late many pathologists are inclined to class as carcinoma, instead of sarcoma—no marked beneficial effects have been noted at any time.

What is the explanation for these variable results? Why should the toxins behave so differently in these cases, causing some of the very worst and most hopeless ones to become permanently cured, and in others showing little or no effect?

The explanation is, I think, not so very difficult. My own belief, expressed sixteen years ago and held more firmly with increasing clinical experience, is that all varieties of malignant tumours are of extrinsic or microbic origin. Just what type of organism this may be—whether bacterium, protozoan, or spirochæte, or what not—is of little consequence. Assuming such origin, we have but to follow the analogy of other diseases of known germ origin. We know that in all such diseases there is a natural immunity and an acquired immunity. In the case of malignant tumours there is probably a natural immunity which is very great, but in certain cases it is absent or becomes lowered, and the germ finds a favourable site and here starts the primary malignant tumour.

The important role that trauma or injury plays in the development of

malignant tumours, now accepted by all authorities, can, to my mind, but be explained on the theory of microbic origin, some writers—*e.g.*, Tillmanns—going so far as to state that most cases of bone tuberculosis follow an antecedent injury, the bacilli, of course, being present in the circulation prior to the injury; but a naturally existing immunity or resisting power of the tissues had been sufficient, up to this time, to prevent any local infection. The injury, lowering this local resistance of the tissues, furnishes precisely the conditions favourable for the growth and development of the bacilli. Hence the origin of the tuberculous lesion.

If time permitted, I could cite many striking cases of sarcoma of the most virulent type that followed immediately upon a blow or an injury to the bone in previously perfectly healthy individuals. The ætiology of tumours is a problem far too difficult and complicated to do more than touch upon here. Assuming such extrinsic origin, the action of the toxins appears to me to produce certain changes in the blood or serum that restore the weakened or lost immunity or natural resisting power of the tissues, and the sarcoma-cell, no longer finding conditions favourable for further growth and development, undergoes a process of degeneration, with absorption in some cases and the formation of a slough in others.

The reason why a cure results in some cases is that in these the antagonistic action of the toxins is sufficient to destroy the cancer-cell and render the soil unfavourable for further growth; whereas in other cases the tumour-cells, by reason of greater vigour or better nourishment, are more resistant and, although receiving a temporary setback by reason of the changes in the blood produced by the toxins, soon accommodate themselves to the new environment and continue to grow as before.

The high temperature produced by the toxins may also be a factor in causing the improvement that follows their use. Many and repeated blood-examinations of sarcoma patients treated with the toxins show almost universally a marked leucocytosis as a result of the treatment.

That the tumour-cell is ever in a delicately balanced state is shown by the experimental investigations upon mouse-cancer during the past four years. A certain strain of carcinoma was found to grow well in Berlin mice, but would not grow at all, or in few cases only, in Danish mice of the same breed. To quote a recent and unpublished paper of Dr. Jones Ewing, "Apparent slight differences in the food supply sufficed to render the soil unfavourable to the tumour-cell. These remarkably delicate nutritional requirements of the cancer-cell suggest

that some means may be found to render the human patient's tissue unfavourable for cancer growth." And this is exactly what, in my opinion, the toxins do in sarcoma.

INDICATIONS FOR THE USE OF THE TOXINS.

While in all my earlier papers I have practically limited the use of the toxins entirely to cases of inoperable sarcoma, further experience has convinced me that they have a much wider field of usefulness. I would at present advocate their use, first, in all cases of inoperable sarcoma, except the melanotic, which are classed as of epithelial origin by many pathologists; second, in cases of sarcoma originating in the long bones in which operation means a sacrifice of the limb: if in these cases no improvement is noted at the end of two to three weeks, I would then advise excision, resection, or amputation, according to the individual case; third, in all cases of operation for primary sarcoma directly after wound healing as a prophylactic against recurrence; fourth, in addition to the foregoing, I think there is good ground for believing that the use of the mixed toxins after all operations for carcinoma would greatly lessen the number of recurrences. This opinion is based partly on the clinical observations of a considerable number of cases in which both epithelioma and carcinoma have entirely disappeared and been permanently cured from attacks of accidental erysipelas, and partly upon the marked inhibitory action of the mixed toxins upon inoperable carcinoma, as shown by actual experiments in a large number of cases.

THE USE OF THE TOXINS IN SARCOMA OF THE LONG BONES.

This deserves special mention. In a recent paper upon the "Conservative Treatment of Sarcoma of the Long Bones," read before the American Medical Association, I gave a detailed study of ninety-two cases of sarcoma of the long bones that had come under my personal observation within the last eighteen years. I stated: "The facts I have set forth are sufficient, in my judgment, to justify the giving-up of the traditional method of treating all cases of sarcoma of the long bones by immediate amputation. In most cases I believe it safe to wait for two to three weeks, the time required for a trial with the toxins, before sacrificing the leg. Sarcoma cases of extremely rapid growth will probably show little or no effect from the toxins, and one might (naturally) say valuable time had been lost by the preliminary use of the

toxins. However, it is my opinion that early operation in these cases would not have been of the slightest avail, as shown by the long, almost unbroken list of fatalities of cases treated by operation alone. On the other hand, in certain cases—probably a small number—the limb will be saved by the preliminary use of the toxins. In those in which early improvement is not marked, operation can then be performed with even greater chances of ultimate success than had the toxins not been first used.

The greatest value of the toxins in sarcoma of the long bones will, I believe, be shown to lie in a judicious combination with conservative operative treatment. By such procedure hip-joint amputation, which has been the almost uniform rule for sarcoma of the femur, will give place to an amputation below the trochanter which will leave a stump of sufficient length to permit the wearing of an artificial limb; and this is no small gain. The toxins will be administered for a considerable period of time after amputation, with the hope of destroying the cells which were left behind, and which, with operative treatment alone, cause the local and metastatic recurrences. The same rules will apply to sarcoma of the humerus.

Coming to sarcoma of the tibia, fibula, and radius and ulna, particularly of the myeloid type, in place of amputation, as formerly advised and still advocated by the great majority of surgeons, we can safely substitute either curetting or partial resection, followed by a thorough course of the mixed toxins. While good results have been obtained in a very limited number of cases in this group by operation alone, I am convinced that the number of successes will be greatly increased by combining the toxin treatment with conservative operation, as I have suggested, and my series of cases strongly supports this opinion.

As earlier diagnosis is steadily but surely coming, owing to increased knowledge of this disease, coupled with more correct interpretation of X-ray plates and the use of earlier exploratory operations, the conservative treatment along the lines I have mentioned will soon show results infinitely superior to those obtained by the radical and maiming operations thus far almost uniformly practised.

The following cases of sarcoma of the long bones are worthy of special note:—

(1) E. D., female, aged 18. Periosteal round-celled sarcoma of femur: amputation below trochanter, followed by toxin treatment for four months. Well at present, three years.

(2) C. L., female, aged 12. Periosteal round-celled sarcoma of femur: amputation below trochanter; toxins for four months after operation. Well three years and nine months.

(3) A. G., male, aged 19. Round-celled periosteal sarcoma of the femur, involving two-thirds of the shaft: hip-joint amputation advised February, 1902, but refused; developed extensive metastases in the pectoral region and a tumour the size of a child's head in the ileo-lumbar region under X-ray treatment; then the mixed toxins of erysipelas and *Bacillus prodigiosus* were given; entire disappearance. Patient well when last seen, six years later. Reported well September, 1909, seven years later.

(4) J. F., male, aged 40. Spindle-celled sarcoma of the tibia, recurrent after extirpation: preliminary use of the toxins before sacrificing the limb; entire disappearance under three months' treatment. Patient well ten years, without loss of leg.

(5) Case of Dr. A. Gerster's—Female. Round-celled myelogenous sarcoma of femur: diagnosis confirmed by Professor T. M. Prudden; too extensive for hip-joint amputation; spontaneous fracture; disappearance under four months' treatment with the toxins; bone reunited. Patient shown before the New York Surgical Society in perfect health four years later.

(6) K. K., female, aged 18. Myelogenous round- and giant-celled sarcoma of tibia: recurred very quickly after two extirpations; finally disappeared under six months' treatment with the toxins plus X-rays. Well four years.

(7) Mrs. F., aged 26. Myelogenous giant-celled sarcoma of lower end of radius: extirpation; amputation advised by Drs. Harlow and Pool: refused; toxins five weeks. Patient well at present, one year.

(8) *Sarcoma of the Femur, Periosteal; four months' duration.*—Mr. W., male, aged 40. Exploratory operation showed it to be round-celled sarcoma: amputation below trochanter, September, 1906, by Dr. Erdman; toxins for five months, under my direction, by Dr. Grausman. Patient well at present, three years later.

(9) *Sarcoma of the Femur, Periosteal; very rapid growth.*—Male, aged 10. Temperature 101° F. to 102.5° F.; exploratory operation; spindle-celled sarcoma, involving two-thirds of the shaft of the femur; toxins given in large doses for eight months; the tumour of the femur nearly disappeared. Patient died of intra-orbital or brain metastases one year later.

(10) *Periosteal Round-celled Sarcoma of the Clavicle.*—Mr. H. Very rapid growth; excision of clavicle by Dr. Maurice H. Richardson, of Boston, May, 1908. Referred to me for the toxins immediately after wound healing. Tissues about the neck suspicious of sarcomatous infiltration; immediately put upon the toxins; continued in large doses for eight months, in all eighty-seven injections; largest dose, 28 mm.; injections made into pectoral region and buttocks. Patient gained 28 lb. in weight, fully recovered his normal health, doing hard

work the last six months. Examination June, 1909, thirteen months afterward; no trace of recurrence. (Dr. Richardson states that if the patient remains well he will attribute his recovery entirely to the toxins.)

These cases become of considerable importance when we consider that recovery from periosteal sarcoma of the femur, treated by amputation alone, is extremely rare. You are all, doubtless, familiar with Mr. Butlin's well-known work upon sarcoma of the long bones, and remember the fact that of his series of sixty-eight cases of periosteal sarcoma of the femur treated by amputation, either at the hip-joint or just below the trochanter, only one was cured.

Dr. Charles B. Nencrede, of Ann Arbor, the President of the American Surgical Association, stated recently that he had performed sixteen amputations at the hip-joint for sarcoma of the femur without a single permanent cure.

THE TOXINS AS A PROPHYLACTIC AGAINST RECURRENCE AFTER OPERATIONS FOR PRIMARY SARCOMA.

The use of the toxins as a prophylactic after operation for sarcoma I believe to offer by far the most important field of all, and one that is gradually being appreciated by the profession. At the Mount Sinai Hospital, in New York, the toxins are now used by Dr. Gerster and Dr. Lilienthal in all inoperable cases of sarcoma as well as a prophylactic after operation for primary sarcoma, and many others are beginning to use them in this way. I have already a sufficient number of cases of sarcoma in which I have used the toxins as a prophylactic measure to justify such use.

The following is a partial list of cases in which the toxins have been used after operation:—

(1) Sarcoma of finger, periosteal, round-celled (Welch): imperfect removal; amputation considered, but a trial of toxins determined; toxins three to four months, systemic chiefly. No recurrence, nine years.

(2) Testis, round-celled (Professor Whitney): recurrent in other testis; castration; toxins after second operation for four months. Patient well at present, over four years.

(3) Testis, round-celled: very rapid growth; castration; toxins three months. Patient well over three years.

(4) Testis (round-celled sarcoma of undescended testis): removal; tumour very large; almost certain that some sarcomatous tissue was left behind; toxins as soon as wound had healed. Patient well one year later.

(5) Humerus: very large tumour, size of a man's head; amputation followed by toxins. Patient well over a year; no trace of recurrence.

(6) Clavicle: excision for rapidly growing round-celled sarcoma of clavicle (microscopical examination, Professor Whitney, Harvard): toxins begun immediately after wound was healed; suspicion of recurrence before toxins were begun; toxins given for one year. Patient in perfect health at present, one year later.

(7) Tibia, round-celled: toxins before and after amputation. No recurrence two years.

(8) Hand: four operations before toxins were given; toxins two months. Patient well six months, when lost sight of.

(9) Sarcoma of metatarsal bone, periosteal, round-celled: rapid growth; amputation; toxins four months after operation. Patient well eight years.

(10) Sarcoma of radius: amputation; toxins three months. Patient well three years.

(11) Sarcoma of femur: amputation below trochanter; toxins four months. Patient well three years.

(12) Sarcoma of femur: amputation below trochanter; toxins four months. Patient well two years and ten months.

(13) Sarcoma of femur: amputation; toxins four months. Patient well two years and nine months.

(14) Sarcoma of kidney, child aged $1\frac{1}{2}$: round-celled nephrectomy: given nearly a hopeless prognosis; toxins used almost two years. Child in perfect health at present, four years.

(15) Sarcoma of femur: amputation below trochanter; toxins six months. Patient still well at present, ten months.

(16) Sarcoma of biceps muscle, round-celled: recurred two to three weeks after excision; toxins after second operation; recurrence delayed, but not prevented; amputation shoulder-joint, January, 1908. Patient in perfect health at present, July, 1909.

(17) Sarcoma of breast: entire breast involved; rapidly growing spindle-celled sarcoma; amputation (Dr. Parker Syms); toxins two months under my direction. Recurrence about six months later; death within the year.

THE TOXINS AS A PROPHYLACTIC AGAINST RECURRENCE AFTER PRIMARY OPERATIONS FOR CARCINOMA.

While I have not sufficient data to enable me to speak emphatically in regard to carcinoma, I believe the inhibitory action of the toxins upon carcinomatous cells—sufficient in an insignificant number of cases

to cure a large inoperable tumour—to be sufficient to prevent recurrence in a considerable number of cases if used after operation. I have had one case in an inoperable epithelioma of floor of mouth and lower jaw (fig. 2). When used as a prophylactic measure in the way I have indicated, I believe the toxins to be entirely devoid of risk. No deaths have occurred in the cases in which the treatment was used as a prophylactic. In these cases the dose given is smaller, and it is not increased to the point of producing severe reactions; a moderate temperature of 99-101° F. is all that is required. This will not in any way interfere with the ordinary routine of life. The toxins can



FIG. 2.

Epithelioma of chin and lower jaw. Well seven years after treatment.

be given for long periods of time without any harmful effects, as is shown by a case of eight times recurrent sarcoma of the chest-wall in which the treatment was continued for four years, and the patient is now well, fourteen years after the beginning of the treatment, or ten years after its cessation. The treatment did not in the least interfere with his regular work. I have several other cases in which the toxins were given for two years or more without any unfavourable effects.

DURATION OF TREATMENT.

It is very hard to lay down any definite rules as to the duration of treatment that would apply to all cases. My own feeling, based upon my experience up to the present date, is that there is much more danger in stopping the toxins too soon than in giving them too long. That they can be given for very long periods without harm is shown by some of my cases, one in particular having taken the toxins with some intervals of rest for a period of nearly four years. He had had eight operations for recurrent spindle-celled sarcoma of the chest-wall. At each operation the tumour had become more malignant, and the case was considered quite hopeless from the standpoint of further operations. The treatment was given in small doses which, after the first few weeks, did not interfere with the performance of the patient's duties as a surgeon. He is to-day in perfect health, fourteen years after the beginning and ten years after the cessation of the treatment. In many of the prominently successful cases the toxins have been given for comparatively short periods—six weeks to three or four months. One, an inoperable sarcoma of the abdominal wall, had only thirty-one injections, and entirely recovered and was well when last seen, one and a half years later. Another case, an inoperable sarcoma of the abdominal wall, spindle-celled, was pronounced hopeless by Professor Maurice H. Richardson, of Harvard Medical School; diagnosis confirmed by microscopic examination by Professor Whitney; disappearance of the tumour under four months' treatment in the fall of 1894. The patient is to-day in perfect health, fifteen years later.

Another case, an inoperable sarcoma of the breast, axillary glands, and pectoral muscle; the diagnosis confirmed by Professor W. H. Welch, of Johns Hopkins; the tumour disappeared after seventy-eight injections (1895), and the patient is still in perfect health. I presented her before the Medical Society of New York in February, 1909, fourteen years later.

Another case of inoperable sarcoma of the abdominal wall and pelvis, involving the bladder, was treated with the toxins for six months (January, 1893). The tumour entirely disappeared, and I presented the patient before the New York Surgical Society in 1898 in perfect health, fifteen years later. In this case the patient had been pronounced inoperable by Dr. L. Bolton Bangs, and the diagnosis of spindle-celled sarcoma was confirmed by Dr. H. T. Brooks, Professor of Pathology at the Post-Graduate Medical School.

In a few cases there has been a recurrence of the tumour after it had once disappeared under the toxins treatment, and I feel that had the toxins been given for a longer time a cure might have resulted. My first case of sarcoma of the neck and tonsil, recurrent and inoperable, was treated with living cultures, finally resulting in a severe attack of erysipelas. The tumours nearly disappeared and the patient entirely recovered his general health, but finally died eight years later from a local recurrence.

In another case of extensive sarcoma of the back, with large metastatic tumours in the groin, the tumours entirely disappeared under living cultures of erysipelas. Recurrence quickly followed, but finally disappeared under the injections of the toxins. Patient remained well for three and a quarter years, when he died of abdominal metastases.

With a very few exceptions (four or five), all cases in which the tumours have disappeared under the toxin treatment have remained well. These few cases of recurrence furnish the most convincing evidence of the undoubted influence of the toxins upon sarcoma, inasmuch as they absolutely prove that, in these cases at least, there could have been no error of diagnosis. Can we, then, form any practical rules to guide us as to how long the toxins should be administered? I would say, give the toxins until the tumours have entirely disappeared, and then continue in smaller doses and greater intervals for three or four months longer. If no improvement is noted at the end of four or five weeks, a successful result is not likely to occur, and retardation of the growth is all that can be expected from a further use of the toxins. A concrete example may be of some help in determining the duration of treatment:—

Recurrent Inoperable Sarcoma of the Back with Metastatic Tumour of the Lower Jaw (large round-celled); entire disappearance under two months' treatment with the toxins; patient well at present, nearly two years later.—Male, aged 35; very large and rapidly-growing sarcoma of the back (lumbar region), for which he had two operations in rapid succession, in September and October, 1907. He had developed a metastatic tumour in the lower jaw, and lost 40 lb. in weight, and was sent home to die by his attending surgeon, Dr. Biddle, of the State Hospital of Pennsylvania. Microscopical examination had been made by the pathologist of the Jefferson Medical School, Philadelphia, who pronounced it a large round-celled sarcoma. The patient was brought to me in November, 1907, greatly emaciated and unable to walk without help. In view of the very rapid growth of the tumour with such early bone metastases I gave a very bad prognosis, but still thought it worth while to try the toxins. The toxins were nearly all given systemically, *i.e.*, into the buttocks; only

4 or 5 doses of the filtered toxins were injected into the tumour of the jaw. He was quite susceptible to the toxins; highest dose he ever received was 8 mm. He was not able to stand more than four or five doses a week. At the end of one month there was slight improvement; at the end of six weeks the improvement was marked; from that time on tumours melted away with great rapidity, until at the end of ten weeks there were no traces left either in the back or jaw. On February 8, 1908, three months after treatment was begun, the patient had regained his lost weight and most of his strength, and was sent home. The toxins were continued by the family physician twice a week for two months, and once a week until July, 1908, since which time he has had no further treatment. No treatment other than the toxins was given during the whole time. I presented him before the New York Orthopædic Association, February, 1908, and examined him a few weeks ago at my office. He has gained 69 lb. in weight, and there is no trace of tumour in any part of his body; he has been performing his regular duties as a manufacturer for now more than a year.

Much depends upon a judicious determination of the dosage for the given case. As a rule I like to give as much as the patient can safely stand. I always begin with one-fourth of a minim diluted with sufficient boiled water to ensure accuracy of dosage, injected either into the buttocks or pectoral region. After the individual's susceptibility has been ascertained, one can inject into the tumour itself if it is in an accessible region. The initial dose into the tumour should always be less, not more, than one-fourth of that used elsewhere. I believe it a good plan to give the injections alternately into the tumour and into the buttocks. Daily injections should be given, increasing by one-fourth of a minim until the desired reaction—namely, a temperature of 102-104° F.—has been obtained. This should be modified to suit patients in a weakened condition. Having secured the desired reaction, the dose should no longer be increased until it fails to give a reaction, when it can again be increased by one-fourth to half a minim. The dose varies greatly with different individuals; the highest dose ever given in many of the cured cases has been 7 mm. to 8 mm. On the other hand, the case of spindle-celled sarcoma of the sternum and cervical glands (microscopic examination by Dr. James Ewing, Professor of Pathology, Cornell University Medical School) showed little improvement until large doses, as high as 30 m, had been given directly into the tumour. The treatment was carried out by another physician, Dr. David John, of Yonkers, New York, under my direction. The tumours entirely disappeared, and the patient is still well, nearly three years later. I presented her before the New York Surgical Society a year ago. I have at present under

treatment at the Hospital for Ruptured and Crippled at New York a little girl, aged 6, with a three-times recurrent sarcoma of the face, in which the dose was carried up to 20 m, injected directly into the tumour, before a marked reaction was obtained. She has now taken the toxins for nearly four months, and under these large doses has shown very marked improvement. When I left the tumour had nearly disappeared, and I am hopeful of a cure. On several occasions the toxins were stopped for a few days, and each time there was a rapid increase in growth. I have never seen a case in which the inhibitory action of the toxins upon sarcoma has been more beautifully demonstrated, whether a cure result or not.

The greatest obstacles to a fair trial of the toxins up to the present time have been: (1) The difficulty of obtaining a preparation of the toxins of uniform standard of strength and efficiency. I will here state that all of my results have been obtained from toxins prepared by Dr. B. H. Buxton, Professor of Experimental Pathology, Cornell Medical School, from 1893 to 1906; from 1906 to the present time by Dr. Martha Tracy, Assistant Pathologist to the Huntington Cancer Research Fund, who received personal instructions from Dr. Buxton in the method of preparing the toxins. Dr. Tracy's own modification of the method of preparation, by means of which it has been possible to standardize a dose, is a marked step in advance. The preparations before this time were much more variable in strength and efficiency. (2) The published failures of a few men who have given the method a limited and most imperfect trial, usually with a preparation of the toxins entirely different from that used by myself. (3) The number of cases of sarcoma is so limited that the ordinary physician or surgeon sees not more than one or two cases a year; even in large hospitals there may not be seen more than five or six cases a year, and these are chiefly operable cases. In these the tumour is removed, patient is sent home until later, when a recurrence has taken place, he is again sent to the hospital. If operable, the tumour is again removed; if not, he is sent home and his physician advised to make his end as comfortable as possible.

Occasionally the physician has heard of the use of the mixed toxins in such cases; if he has read of the method, he has probably forgotten the details and has little faith in its value. Now and then a surgeon is found who takes the time to give the matter special thought, and who is willing to give the patient the benefit of a trial with the toxins. He begins with some fears and more doubts, and when he sees the patient in one of the severe chills, sometimes with marked cyanosis, very rapid

and feeble heart action, with a temperature of 103.5° F., he hesitates to go on, or is unable to instil into the patient the courage and confidence so necessary to enable him to continue the treatment to a successful termination. For these or other reasons injections are stopped and the treatment pronounced a failure.

DANGERS OF THE TOXINS.

The risks of the treatment have been unduly emphasized. While I have personally found the administration of the mixed toxins practically free from danger, there have been several fatal cases in the hands of other physicians brought to my notice which, taken together, show that there are certain risks connected with the treatment. If, however, the precautions which I have always carefully emphasized in former papers be observed, these risks, I believe, will be reduced to a minimum. Most of the fatal cases that have occurred have been due to a neglect of these precautions. In my own experience in nearly 500 cases there have been only three deaths.

In the majority of the fatal cases thus far observed death was apparently due to an embolism. This was the cause in two of my own cases, and in both instances the general condition of the patients was extremely bad; there was generalization of the disease and very marked involvement of the mediastinal glands. In both cases the patients had only very small doses of the toxins, which were not pushed to the point of giving any marked reactions.

Most of the deaths in the hands of other men have been due, I believe, to too large an initial dose given directly into a vascular primary growth. In recent years I no longer inject the initial dose directly into a tumour, but first test the individual susceptibility of the patient by systemic injections in the buttocks or pectoral region; after a few such injections local treatment may be begun, always starting with a minimum dose. I rarely give more than $\frac{1}{6}$ mm. into the tumour in children, especially if situated in the neck or mediastinum, and never more than $\frac{1}{4}$ mm. in adults. I have seen a temperature of 105° F. result from $\frac{1}{5}$ mm. injected into a large cervical tumour in a child. In one of the fatal cases in the hands of other men death resulted from an injection of $\frac{1}{4}$ mm. of Dr. Tracy's early preparation (twice as strong as at present) directly into a mediastinal tumour. This was an elderly woman of very feeble vitality.

Another case, recently brought to my notice by the physician in charge, contains an important lesson—*i.e.*, that the toxin should never be administered by any physician who is not willing to give sufficient time, I will not say to thoroughly read all of the literature connected with the treatment, but at least the directions upon the bottle. In this case the initial dose was 5 mm. injected into a vascular tumour. The physician stated that he had turned the case over to his assistant, who gave him 5 mm., and the patient died in fifteen minutes. Death might also have resulted had he given him 20 gr. of morphine, though perhaps not so quickly. The toxins are, indeed, like strychnine and morphine, safe if judiciously and intelligently administered, but exceedingly dangerous if given in the way described.

I have known of another instance, a case of sarcoma of the lower jaw, in which—after two operations had been performed and it was not thought that the disease had been entirely removed—the toxins were advised immediately after operation. In this case, also, the treatment was turned over to an assistant. Although never within the last fifteen years have the directions sent out with the toxins called for larger initial doses than $\frac{1}{4}$ mm. or $\frac{1}{2}$ mm., the assistant in this instance proceeded to give 20 mm. as a first dose. This was some years ago, when the preparation was considerably weaker than at present; at least its strength was more variable. Although the patient went into coma and remained comatose and delirious for some time, he finally recovered and is well now, two years afterwards, the tumour of the jaw having been cured.

In a few other cases, however, in which death resulted, the ordinary precautions had apparently been carried out. One such case was seen by myself in consultation, and the treatment advised and a general outline of the dosage given. This was a woman, aged 55, with a very large, vascular sarcoma of the ilium. Her general vitality was much impaired and circulation not good. The toxins were begun in minute doses, $\frac{1}{4}$ mm., and gradually increased up to the point of reaching a temperature of 103-4° F. After about two weeks' treatment, an injection of 12 mm. caused a severe chill; the patient became very weak and exhausted, and did not recover. In this case, had I had personal charge of it, I have no doubt that, seeing that she did not bear the toxins well and that the temperature remained high, I should not have increased the dose as rapidly as was done.

Each case must be treated on its individual merits. In one case death resulted from increasing materially a dose which, the day before,

had already produced a severe reaction, the patient still having a temperature of 102° F. at the time the injection was given. It is a very good rule not to repeat injections as long as the patient has any material rise of temperature, but to wait until the latter has fallen to normal or nearly normal. After the desired reaction is obtained, causing a temperature of 102-3-4° F., according to the vitality of the patient, one should not increase the dosage until it has failed to produce such reaction. I have never known of a fatality from the use of the toxins as a prophylactic after operation, nor of any dangerous symptoms.

FINAL RESULTS.

Up to the present time I have had fifty-two cases of inoperable sarcoma successfully treated with the mixed toxins of erysipelas and *Bacillus prodigiosus*. Of these, thirty-five have remained well from three and a quarter to sixteen years; twenty-eight from five to sixteen years, and fourteen from ten to sixteen years. To the thirty-six successful cases published in the *American Journal of the Medical Sciences*, in March, 1906, I have been able to add sixteen others.

In the first thirty-six cases reported in 1906 there was, in addition to the tumours being adjudged inoperable by leading surgeons, a careful microscopical diagnosis made in all but two instances. One of these cases was a large tumour of the sacrum, pronounced sarcoma and inoperable by the attending physicians and surgeons of St. Luke's Hospital of New York. The patient had lost 40 lb. in weight and could not walk without assistance. The tumour entirely disappeared under two months' treatment with the mixed toxins; in three months he had regained his normal weight and resumed his work. He is well at the present time, fourteen years later. The other case was a large inoperable tumour of the right iliac fossa, highly vascular, pronounced sarcoma by Dr. G. R. Fowler, of Brooklyn, after an exploratory laparotomy. The tumour disappeared under the toxin treatment, and the patient remained well for eight years, when he died of another disease.

The majority of these cases have been shown from time to time before the New York Surgical Society, one of them sixteen years after treatment. At the Hartford Medical Society last year I showed three cases, all residents of Hartford. One, an enormous sarcoma of the gluteal region, well for fourteen years, was recurrent and had been

pronounced inoperable by Dr. Charles McBurney when I began the treatment. The second case was a spindle-celled sarcoma of the breast and pectoral region; diagnosis confirmed by Dr. W. H. Welch, of Johns Hopkins Medical School; treated under my direction at Hartford; well fourteen years. The third case was a round-celled sarcoma of the tonsil and larynx, with metastases in both cervical regions. Entire disappearance under six months' treatment; well at present, nearly three years afterwards; diagnosis confirmed by microscopical examination, Cornell Medical Schools Laboratory.

In my paper of April, 1906, *American Journal of the Medical Sciences*, I tabulated the successful cases of other men, sixty in number. Since that time, from personal communications and published reports, this number has greatly increased, until now I believe that considerably more than 100 cases have been successfully treated by other surgeons. I am much gratified to find two successful cases, recently reported in the *Lancet*, March 20 and May 22, 1909.

I cannot give in detail all of my successful cases. This would require too much space, and the majority have already been reported in my paper published in the *American Journal of the Medical Sciences*, March, 1906, and in the *Annals of Surgery*—Transactions of the New York Surgical Society—since that date. I believe, however, that it may be of sufficient interest to give a brief history of a few of these cases, together with a brief abstract of the entire number:—

(1) *Inoperable Spindle-celled Sarcoma of the Abdominal Wall; entire disappearance under two and a half months' treatment with the filtered and unfiltered toxins; patient perfectly well at present, fourteen years afterward.*—Upon this patient exploratory laparotomy was performed in August, 1893, at the Massachusetts General Hospital, by Dr. Maurice H. Richardson, now Professor of Surgery at the Harvard Medical School. The tumour was found to involve such a large portion of the abdominal wall that removal was quite impossible. A portion was excised and examined by Dr. W. F. Whitney, pathologist of the Massachusetts General Hospital, who pronounced it spindle-celled sarcoma. The patient was referred to me by Dr. Richardson in October, 1893, and immediately put upon the injections of the mixed toxins. After her return home, two and a half months later, she had no further treatment, and she has remained perfectly well up to the present time.

(2) *Spindle-celled Sarcoma of the Scapular Region, involving a large part of the left half of the Thoracic Wall.* (Diagnosis confirmed by microscopic examination made by Dr. H. T. Brooks, Professor of Pathology at the Post-graduate Hospital.)—The patient was admitted to the New York Cancer Hospital on January 20, 1894. The tumour entirely disappeared under three

months' injections with the mixed unfiltered toxins, by absorption, without any breaking down. The patient was in good health when last heard from, in 1904, ten years later. (Figs. 3, 4, 5.)

(3) *Inoperable Recurrent Angiosarcoma of the Breast, treated with the Mixed Toxins of Erysipelas and Bacillus prodigiosus.*—The patient, aged 59, had a three-times recurrent sarcoma of the left breast of such size that operation was entirely out of question (fig. 6). The patient was referred to me by Dr. G. F. Shrady, of New York, as an inoperable case. She was admitted to the



FIG. 3.

Spindle-celled sarcoma of scapula and chest-wall. Tumour 13 in. vertically behind, 7 in. vertically in front, adherent to chest-wall. Arm could only be raised to right angle. Photograph taken before treatment.

New York Cancer Hospital, January 20, 1895, and placed in the incurable ward. The diagnosis was confirmed by microscopic examination made by Professor T. M. Prudden, of the Medical Department of Columbia University, who pronounced it a round-celled angiosarcoma. Under the toxin treatment the patient recovered and remained well until 1903, eight years afterwards, when she

fell downstairs and received an injury which proved fatal. She was examined at this time by my associate, Dr. W. A. Downes, who found no trace of a recurrence. (Fig. 7.)

(4) *Mixed-celled Sarcoma of the Parotid, three times recurrent, treated with the Mixed Toxins for six months: patient perfectly well, eleven years later.*—The patient had been previously operated upon by Dr. William T. Bull, who



FIG. 4.

Showing entire recovery. Patient well twelve years after treatment.

referred her to me for the toxin treatment in 1895, as there was no hope of benefit from further operation. She was treated for four months. The tumour slowly decreased in size until there was only a very small freely movable nodule left, about the size of a hazel-nut. This was excised, and careful microscopic examination showed no trace whatever remaining of sarcoma. The patient remains in perfect health at the present time, eleven years later.

(5) *Spindle-celled Sarcoma of the Iliac Fossa, probably involving the Ilium.*— Mrs. D., aged 40, noticed pain in the right iliac fossa in the early part of 1895, and in May discovered a tumour in this region. This steadily increased in size, and on October 19, 1895, Dr. Johnston, of Boston, performed an exploratory laparotomy. His description of the condition found is as follows: “A tumour was found in the right iliac fossa about the size of a cocoanut, attached to the ilium as well as to the abdominal wall, and totally inoperable.



FIG. 5.

Back view of patient shown in fig. 4.

Its exact point of origin could not be made out, but from the exploration and subsequent examination I am convinced that it started from the inner portion of the crest of the ilium.” A part of the tumour was excised and examined by Dr. William F. Whitney, pathologist to the Massachusetts General Hospital and Instructor in Pathology in the Harvard Medical School, who pronounced it spindle-celled sarcoma. In November, 1895, Dr. F. Cobb, of Boston, started the injections with the mixed unfiltered toxins, and at the end of six weeks, as

Dr. Cobb states, the growth had entirely disappeared. In the spring of 1896, however, the patient developed a local recurrence, and on May 17, 1896, she was sent to me for treatment, and was admitted to the New York Cancer Hospital. At this time examination showed a hard mass on the right side extending from the crest of the ilium nearly to the umbilicus and as far to the left as the median line. The tumour was apparently located in the ilium and abdominal wall. The toxins were given, with occasional intervals of rest, for three months, during which time the tumour had decreased to one-fifth of its original size. I then gave her a rest of two months, when she was readmitted to the hospital. During this interval the tumour had increased considerably



FIG. 6.

Recurrent angio-sarcoma (round-celled).

in size, but again began to yield immediately after renewed treatment. She remained under treatment until June, 1897, at which time the tumour had almost entirely disappeared, and examination a few months later showed no trace of it left. I made a personal examination of the patient in the latter part of 1907, at which time she was perfectly well, more than ten years after the cessation of the treatment. During this entire time she led a very active life, supporting a large family of children. Careful palpation failed to show any evidence whatever of the tumour.

(6) *Round-celled Sub-periosteal Sarcoma of the Femur, involving lower two-thirds of the Shaft, with extensive Metastases.*—A. G., aged 19. A tumour in the lower portion of the femur was first noticed in November, 1901. There was no history of trauma. This tumour gradually increased in size, and was accompanied by loss of weight and deterioration of general health. The patient was referred to me on February 5, 1902, by Dr. W. R. Townsend, of the Hospital for Ruptured and Crippled. Physical examination at that time showed a large tumour occupying the entire lower two-thirds of the left femur, fusiform in shape, and most prominent in the region of the condyles. On the



FIG. 7.

Disappearance of tumour under toxins. Patient well eight years later.

outer aspect of the thigh, about $1\frac{1}{2}$ in. above the joint, there was a soft fluctuating area. There was slight impairment of the functions of the joint, but the joint itself was not involved. An incision was made under ether anæsthesia over the fluctuating area, and 3 oz. of clear serum, similar to that found in sarcoma of the bone which has undergone cystic degeneration, was evacuated. By means of a curette a considerable portion of typically sarcomatous tissue was removed. This was examined microscopically by Drs. E. K.

Dunham, of Bellevue Hospital, and B. H. Buxton, of Cornell University, and pronounced small, round-celled sarcoma. The patient absolutely refused amputation at the hip-joint, which I strongly urged. I was at this time just beginning to try the X-ray treatment of inoperable malignant tumours, and gave the patient four exposures a week. At the end of one month the tumour had decreased in size 1 in. The treatment was continued during the entire summer and fall of 1902. The patient gained considerably in weight, but in December, 1902, developed a metastatic tumour in the left pectoral region. This grew very rapidly, and when it had reached the size and thickness of the hand, I removed it with scissors and curette, under ether anæsthesia. Shortly after this, a large tumour, about the size of a child's head, developed in the ilio-lumbar region on the right side; it filled up the whole iliac fossa and extended up to the ribs. I then put the patient upon large doses of the mixed toxins of erysipelas and *Bacillus prodigiosus*. After about four weeks the tumour in the ilio-lumbar region began to soften and break down. As soon as fluctuation became distinct, I made a posterior opening and evacuated a large amount of necrotic tumour-tissue. A tube was kept in place and the sinus drained for about a year. No X-ray treatment was applied to the ilio-lumbar tumour. The sinus in the leg has persisted up to the present time; examinations of several curettings have failed to show any evidence of sarcoma. At the present time, over seven years from the beginning of the treatment, the patient is apparently in perfect health, and there is no longer any evidence of sarcoma to be found.

(7) *Myelo-Sarcoma of the Lower End of the Tibia, twice recurrent; disappearance under eight months' treatment with the mixed toxins.*—K. K., female, aged 21. Admitted to the Hospital for Ruptured and Crippled, September, 1904; operated upon October 11, by Dr. V. P. Gibney. The entire lower third of the tibia was involved, only a thin outer shell being left, as shown by X-ray photographs. A second operation was done January 5, 1905, consisting in the removal of a large mass of sarcomatous material with chisel and curette. At neither operation was any attempt made to remove the entire tumour. After the second operation the patient was put upon the mixed toxins and, a few weeks later, the X-rays were given in addition to the toxins. At first there was some increase in size, but later, under large injections, followed by more severe reactions, the tumour was held in check and, finally, slowly receded. The treatment was continued until July, 1905, by which time the tumour seemed to have disappeared entirely. The patient has remained in perfect health, without any sign of recurrence, up to the present time, four and a half years later. The microscopical examination in this case was made by Dr. F. M. Jeffries, Professor of Pathology to the New York Polyclinic. The patient was shown in perfect health before the Medical Association of Greater New York, February 15, 1909, and is well at present, September 1, 1909.

(8) *Spindle-celled Sarcoma of the Sternum.*—Mrs. G., aged 38. Mother died of tumour of brain twelve years ago. Past history: In June, 1906, first noticed

enlargement of upper portion of sternum, especially marked over sterno-clavicular joint on the right side. This slowly increased in size, and in December, 1906, I was called to see the patient in consultation with Dr. John, of Yonkers. I advised an exploratory operation to confirm the clinical diagnosis of sarcoma. This was performed on December 29, 1906, and the specimen removed was examined by Dr. James Ewing, Professor of Pathology of Cornell University Medical School, and Drs. B. H. Buxton and Martha Tracy, of the Loomis Laboratory, who pronounced it spindle-celled sarcoma. On January 6, 1907, the mixed toxins were begun by Dr. John under my direction. The treatment was given every other day in gradually-increasing doses; by the end of January the dose had reached $2\frac{1}{2}$ mm., which was followed by a temperature of $103-4^{\circ}$ F. After twenty injections had been given the tumour had diminished considerably in size, and the treatment was suspended for two weeks. At the end of this time examination showed the tumour to have increased again, and a small lump was observed beneath the sterno-mastoid muscle. The injections were continued at varying intervals for six months until June, 1907, the highest dose given being 30 mm. injected directly into the tumour. The tumours slowly decreased in size, even after the cessation of the treatment, and finally disappeared, and the patient at present—August 10, 1909—has had no recurrence. Her physician, Dr. John, writes me, August 10, 1909, that she suffers from periodic headaches, and has fallen on one or two occasions. This may mean brain metastasis, or it may be an independent condition.

(9) *Sarcoma of the Ilium*.—N. G., male, aged 13. Family history, good. Past history: Fell downstairs two years ago, striking left pelvic region; in bed about two weeks; fell again a year later, striking same side; laid up in bed for three weeks. Soon noticed some swelling in region of left ilium, which gradually increased in size; during last six months there has been some slight loss of flesh and decline in general health. Patient referred to me by Dr. La Ferté, of Detroit, in August, 1906. Physical examination at this time showed a tumour involving almost the entire left ilium, being hard in some and soft in other places; considerable limitation of motion in the left leg, marked loss of flexion of left thigh; has had some pain during last year, which at times was paroxysmal. The patient was admitted to the General Memorial Hospital in August, 1906, and put upon the mixed toxins; the treatment was continued for a little over a year, with two intervals of a few weeks' rest; highest dose, 8 mm. The injections were made into the buttocks rather than into the tumour. The swelling gradually decreased and limitation of motion nearly disappeared. At the end of a year the tumour had practically disappeared, although there remained some enlargement, apparently due to the new-bone formation, as often seen in osteo-sarcoma. I examined the patient in June, 1909, and he remains at present in perfect health, three years later.

(10) One of the most remarkable results yet obtained was a case of inoperable round-celled sarcoma of the upper jaw with metastases, successfully treated by Dr. O. K. Wineberg, of Lake Park, Minn., published in the *Medical Record* of May 3, 1902. The patient was so desperately ill at the beginning

of the treatment that no photograph could be taken until he had had sixty-three injections and the tumour had greatly improved, having diminished to one-half its original size (figs. 8, 9). At the time the treatment was begun the man weighed 113 lb.; he was jaundiced, cachectic, and the abdomen markedly swollen; pulse 165, weak and irregular; he was not expected to live but a few days. The important feature of this case is that all the injections were given systemically, either into the abdominal wall or into the arm. At the end of three weeks the jaundice disappeared, as also the metastases in the axillary region; there was marked decrease in the size of the tumour of the jaw: the



FIG. 8.

Round-celled sarcoma of upper jaw, with abdominal metastases. Photograph after sixty-three injections; tumour had diminished to about half original size.

toxins were given in as large doses as the patient could bear, from August, 1901, to January, 1902—103 injections in all. In three weeks he had gained 11 lb.; in four weeks he resumed his work as veterinary surgeon. Four months after treatment he made a trip to New York to show me the result, and I presented him before the Surgical Section of the New York Academy of Medicine. The diagnosis in this case was further confirmed by microscopical examination made by Dr. William H. Welch, of Johns Hopkins University, and Dr.

James Ewing, Professor of Pathology at Cornell University. The patient had remained in perfect health six years later.

(11) *Inoperable Round-celled Sarcoma of the Ovary; Inoperable Tumour made Operable by Toxin Treatment.*—Mrs. E., aged 32. Exploratory laparotomy November, 1904, revealed a large immovable tumour filling up the whole pelvis and extending above the umbilicus. Tumour was exceedingly vascular. A portion of the specimen was removed for the pathological report of the Government Laboratory at Manila. This report read as follows: "An apparently rapidly growing and infiltrating, very cellular growth of probably perithelial origin; perithelial hemangiosarcoma." The patient was admitted to



FIG. 9.

Photograph taken after three months' treatment; tumour had diminished to one-third original size. Patient well nine years later.

the General Memorial Hospital in the service of Dr. Henry C. Coe, attending gynaecologist to the General Memorial Hospital, February 20, 1905. The opinion of Dr. Coe and the others who saw her was that the tumour was clearly inoperable. The tumour, which filled up the entire lower abdomen, extending above the umbilicus, was firmly fixed. The case was turned over to me by Dr. Coe for treatment with the toxins, which were given from February 24 to May 31, forty-seven injections in all. In addition to the toxins, the patient had twenty-two X-ray exposures. There was a very slow diminution in the size of the tumour, with marked increase in mobility, so much

so that it was thought possible that the tumour could be removed by another operation. Operation performed June 12, 1905, by Dr. Coe. A tumour the size of a child's head was found, originating in the right ovary. It was entirely free from adhesions. No metastases were found. The tumour was very easily removed, the entire operation not taking longer than fifteen minutes. The effect of the treatment was very good, as shown by the pathological report by Dr. Tracy: "The tumour within was very much degenerated, the contents being almost of a puriform consistence. Therefore it was difficult to fix and stain, and the diagnosis is not clear. Dr. Ewing is unwilling to say whether it is sarcoma, endothelioma, or carcinoma, though of the malignancy there is no doubt."

The report of a less degenerated portion of the tumour by Dr. Clark, the pathologist to the General Memorial Hospital, was round-celled sarcoma, which corresponded with reports of specimens removed before treatment. The patient made an uninterrupted recovery, gaining 28lb. in weight within six months, and



FIG. 10.

Inoperable sarcoma of sacrum. Treatment for six months. Patient well fourteen years later. (See Case 10, p. 37).

returned home in perfect health. Within six months she conceived, and gave birth to a healthy child in summer, 1906. She remained well up to the latter part of January, 1907, when she contracted pneumonia, and died within a few days. While the patient had not remained sufficiently well to be classed as a cure, complete restoration to health and prolongation of life for nearly two years make it worthy of note. It is possible that the supposed attack of pneumonia may have been due to metastases in the lungs. The chief interest in the case lies in the fact that an inoperable and very vascular sarcoma of the ovary, under a three months' treatment with the toxins, was transformed into a degenerated mass of almost puriform consistence, easily removable by operation.

Table of Personal Cases of Complete or Partial Success, with Late Results.¹

No.	Age	Sex	Date	Locality	Type of tumour	Treatment, duration	Result (immediate)	Result (final)
1	35	M.	May, 1891	Neck and tonsil, recurrent, inoperable	Spindle-celled	Repeated injections of living cultures, four months; one attack of erysipelas	Tumour nearly disappeared, general health restored	Patient lived eight years, and then died of recurrence
2	40	M.	April, 1892	Back and groin, recurrence, inoperable	Mixed-celled (round and oval)	Living cultures of erysipelas; four attacks of erysipelas; finally toxins	Entire disappearance (<i>vide text</i>)	Patient remained well three and a half years, then died of abdominal metastasis
3	17	M.	January, 1893	Abdominal wall and pelvis, inoperable	Spindle-celled	Mixed toxins (filtered); erysipelas and <i>Bacillus prodigiosus</i>	Entire disappearance in four months' treatment	Patient in perfect health sixteen years later
4	29	F.	October, 1893	Abdominal wall, inoperable	Spindle-celled	Mixed toxins three months (Buxton)	Entire disappearance	Patient in perfect health at present, sixteen years later
5	17	F.	January, 1894	Leg, popliteal and space, recurrent; osteo-sarcoma of foot	Spindle-celled	Mixed toxins (Buxton)	Entire disappearance, recurred one and a half years; amputation below trochanter, recurred in gluteal region; finally disappeared under continued toxin treatment	Patient well in December, 1905, twelve years from beginning of treatment, ten years since end
6	34	F.	June, 1894	Chin, lower jaw, floor of mouth, inoperable	Epithelioma (microscopic examination)	Mixed toxins three months (Buxton)	Entire disappearance	Patient well when last heard from, six years later
7	16	F.	June, 1894	Chest-wall, very extensive, inoperable	Spindle-celled	Mixed toxins four months (Buxton)	Entire disappearance	Patient well, 1907, thirteen years later
8	24	M.	March, 1904	Chondrosarcoma of ilium, very large	Chondrosarcoma	Mixed toxins (Buxton)	Entire disappearance	Recurred seven months later and finally proved fatal
9	24	F.	October, 1894	Sarcoma of mesentery, and gall-bladder	Round-celled	Mixed toxins five months (Buxton)	Entire disappearance	Patient well, January, 1908, fourteen years

10	38	M.	March, 1895	Sacrum, inoperable	No microscopic examination, but inoperable tumour of sacrum examined by several surgeons	Mixed toxins six months (Buxton)	Entire disappearance in three months; patient gained 40 lb. in weight	Patient well, January, 1906, twelve years later
11	30	F.	1893	Gluteal region, inoperable, recurrent	Spindle-celled	Mixed toxins three months (Buxton)	Entire disappearance	Patient in good health, no recurrence, December, 1905, twelve years later
12	40	F.	Nov., 1895	Intra-abdominal, inoperable, size of child's head	Spindle-celled	Mixed toxins, three periods of about two months each	Tumour disappeared, and again disappeared under further treatment	Patient in perfect health, January, 1909, fourteen years later
13	16	M.	October, 1893	Sarcoma of pharynx, inoperable	Spindle-celled	Mixed toxins (unfiltered) eight months (Buxton)	Entire disappearance	Patient well when last heard from, six years later
14	20	F.	Feb. 18, 1896	Hand	Spindle-celled	Mixed toxins eleven months (Buxton)	Entire disappearance in two months	Recurred two years later, yielded for a time to further treatment, finally grew rapidly and proved fatal in another year
15	55	M.	1893	Iliac fossa	Round-celled	Mixed toxins two months (Buxton)	Entire disappearance	Patient well one year later, which last seen
16	18	F.	1897	Abdominal wall	Spindle-celled	Mixed toxins, thirty-one injections (Buxton)	Entire disappearance	Patient well one and a half years later, when she returned to Germany
17	59	F.	1895	Breast, recurrent, inoperable	Round-celled, angio-sarcoma	Mixed toxins six months (Buxton)	Entire disappearance with exception of small nodule, which was removed for pathological examination	Patient well over eight years, no recurrence
18	37	M.	1894	Chest-wall, eight times recurrent	Spindle-celled, very vascular	Mixed toxins (filtered and unfiltered), (Buxton)	Disappearance, two or three small nodules removed in first three years	Patient in perfect health, September, 1909, fifteen years later
19	5	F.	1897	Sarcoma of lower lip, three times recurrent	Small round-celled	Mixed toxins six weeks (Buxton)	Entire disappearance	Patient well twelve years later

From Amer. Journ. Med. Sci., Philad., 1906, N.S., cxxxi, pp. 375-430. Corrected to date, September, 1909.

No.	Age	Sex	Date	Locality	Type of tumour	Treatment, duration	Result (immediate)	Result (final)
20	32	F.	1897	Sarcoma of parotid, three times recurrent	Mixed-celled	Mixed toxins six months (Buxton)	Disappearance except small nodule excised, no longer traces of sarcoma	Patient in perfect health, with no recurrence, Jan. 1908, eleven years
21	41	M.	1897	Sarcoma of parotid, recurrence, inoperable	Spindle-celled	Mixed toxins four months (Buxton)	Entire disappearance	Patient free from recurrence six years afterward, when he suddenly died of gastric hemorrhages
22	35	M.	Feb., 1898	Tibia, recurrent, inoperable except by amputation of thigh	Spindle-celled	Mixed toxins three months (Buxton)	Entire disappearance	Patient well at present, July, 1909, eleven years later
23	16	M.	1897	Very large and vascular	No microscopic examination, exploratory laparotomy (Dr. G. R. Fowler, New York)	Mixed toxins several months	Entire disappearance	Patient well eight years later, when he died of other trouble
24	44	F.	1894	Sarcoma of spine, inoperable, recurrent	Spindle-celled	Mixed toxins two months	Entire disappearance	Patient reported well eight years later
25	52	M.	October, 1900	Parotid, recurrent	Round-celled, microscopic examination by Prof. W. H. Welch of Johns Hopkins	Mixed toxins nine months	Entire disappearance	Patient in perfect health six years, and then died of other trouble
26	35	M.	1902	Pectoral region and axilla, inoperable, size of two fists	Round-celled	Mixed toxins three months, later toxins and X-ray	Nearly disappeared before X-rays began, later all disappeared	Recurred one year later. Again disappeared; recurred and finally proved fatal, September, 1905
27	8	M.	1902	Back, recurred three times	Small round-celled	X-ray at first failed, mixed toxins later	Entire disappearance	Patient well, no recurrence September 1, 1909, seven years
28	38	F.	May, 1901	Abdominal wall, involving bladder wall	Fibro-sarcoma	Mixed toxins four months	Entire disappearance	Patient perfectly well January, 1908, seven years

29	16	M.	Feb., 1902	Sarcoma of femur, lower two-thirds, with extensive multiple metastasis	Small rounded	X-rays eight months for primary tumour, metastasis developed in pectoral region and iliac fossa, mixed toxins nearly a year	Entire disappearance	Patient apparently free from sarcoma in any region, September 1, 1909, seven years
30	20	M.	Feb., 1902	Spine, dorsal, very large	Round-celled, paralysis of bladder and rectum and lower extremities, loss of 60 lb. weight	Mixed toxins (Buxton) four months	Entire disappearance	Patient able to walk without crutches in eight months, and without cane in one year; perfect health at present, seven years later
31	56	M.	Feb., 1904	Chest, three times recurrent	Spindle-celled	Mixed toxins (Buxton and Parke, Davis)	Partially removed by operation, disappeared entirely	Patient well without recurrence nearly two years
32	16	M.	May, 1904	Chest-wall, ribs, and pleura	Round-celled, very vascular	Mixed toxins and X-ray (Buxton and Parke, Davis)	Entire disappearance in six months	Recurred in seven months and increased in spite of renewed treatment; death October, 1905
33	28	F.	October, 1903	Intra-abdominal involving mesentery, size of child's head	Small rounded, examined by Prof. W. F. Whitney, Harvard Medical School	Mixed toxins (Buxton and Parke, Davis) with X-ray	Entire disappearance, sudden high temperature with signs of peritonitis, development of faecal fistula, recovery	Small mass felt other side of abdomen one year later (died within six months)
34	34	M.	October, 1905	Tonsil and neck, recurrent, size of half orange	Small rounded	Mixed toxins (Buxton), toxins eight months old, injection local and in pectoral region	Entire disappearance in six weeks, X-ray and radium previously tried and failed	Patient well at present, September, 1909, four years
35	42	F.	1895	Breast and pectoral region, inoperable	Spindle-celled, microscopic examination confirmed by Prof. W. H. Welch, of Johns Hopkins	Mixed toxins (Buxton), seventy-eight injections (local)	Entire disappearance	Patient well August, 1909, fourteen years later
36	18	F.	1905	Tibia, recurrent twice	Round-celled	Mixed toxins five months, with X-rays part of time	Tumour disappeared	A small ulcer remained at last observation, July, 1909, four years

¹ In this case the treatment was carried out under my frequent direction by Drs. Storrs and Griswold, of Hartford, Conn.

*Brief Report of Successful Cases not included in the Tabulated Report of the 1906 Paper*¹:—

(1) *Three-times Recurrent Spindle-celled Sarcoma of Cheek*.—Q., male, aged 50. Mixed toxins; entire disappearance under two months' treatment. Perfect health August, 1909, five years later.

(2) *Large, Recurrent, Inoperable Tumour of Pelvis* (pronounced sarcoma by Dr. Stannard).—M. L., female, aged 50. Operation at the Post-Graduate Hospital in 1894; impossible to remove tumour. Portion received for microscopical examination. Marked decrease in size under four months' treatment with the mixed toxins; then a second futile attempt to remove the growth was made by Dr. Coe and myself. The tumour slowly disappeared without further treatment. Patient shown before the Medical Society of Greater New York in February, 1909, by myself. Perfectly well fifteen years later.

(3) *Recurrent, Inoperable Round-celled Sarcoma of the Neck* (diagnosis confirmed by microscopical examination made by Dr. W. R. Steiner, pathologist to the Hartford Hospital).—A. P., female, aged 2 years 10 months. Tumour recurred two weeks after first operation; again removed; microscopical examination again showed typical round-celled sarcoma; entire neck involved, from mastoid to clavicle. In March, 1902, the toxin treatment was begun and carried out by Dr. M. McKnight, of Hartford, Connecticut, under my direction for six weeks. The tumour entirely disappeared, and the patient is perfectly well at present, seven years later.

(4) *Very extensive Round-celled Sarcoma of the Back, Lumbar Region, twice Recurrent within a few weeks*.—C. E. C., male, aged 30. Metastases in the lower jaw; marked emaciation; extreme weakness; entire disappearance under two and a half months' treatment with the toxins. Patient well at present, nearly two years; gained 69 lb. in weight.

(5) *Primary Sarcoma of the Tonsil involving Pharynx, nearly blocking up Fauces; Metastases in the Neck on both sides; pronounced Inoperable by half a dozen physicians*.—A. L., female, aged 11. Treatment with the mixed toxins begun November, 1906, continued with intervals of rest until May, 1907, between eighty and ninety injections being given, nearly all in the pectoral region, a few in the tumour of the neck, none in the tonsil. Microscopical examination of the tissues removed from both tonsil and neck showed the growths to be round-celled sarcoma. The patient was very susceptible to the toxins; 2 mm. to 3 mm. was the highest dose given; this would produce a temperature of 103° F. to 106° F. Entire disappearance. Patient perfectly well at present, nearly three years.

(6) *Spindle-celled Sarcoma of the Sternum; Metastases in the Glands of the Neck* (diagnosis confirmed by microscopical examination made by Dr. James

¹ *Amer. Journ. Med. Sci.*, Philad., 1906, N.S., cxxxi, pp. 375-430.

Ewing, Professor of Pathology, Cornell University).—Mrs. G., aged 40. Treatment carried out under my direction by Dr. David John, of Yonkers; as high as 30 mm. given directly into the tumour; very severe reactions; showed little improvement until large doses were reached. Treatment continued for nearly six months; entire disappearance. Patient well at present, over three years.

(7) *Sarcoma of the Radius, Round-celled (giant); Spontaneous Fracture; Exploratory Operation with Curetting.*—Mrs. F., aged 26. Amputation advised by Dr. Frank Hartley and Dr. E. H. Pool, of the New York Hospital, in May, 1908; refused; mixed toxins for five weeks. Perfectly well at present, fifteen months afterward.

(8) *Sarcoma of the Ilium, very extensive, Inoperable.*—N. G., male, aged 13. Referred to me as an inoperable case by Dr. La Ferté, of Detroit, Michigan, in August, 1906. Intestinal trouble two years before; almost entire left ilium involved; toxins continued with intervals of rest for nearly a year; almost complete disappearance of the tumour. Patient in perfect health at present, three years later.

(9) *Spindle-celled Sarcoma of the Gluteal Region, Recurrent, Inoperable.*—F. L., female, aged 48. Apparent disappearance under three months' treatment; recurrence in pelvis the following year; inoperable; no further treatment.

(10) *Sarcoma of the Neck (Hodgkin's Disease).*—G. K., male, aged 20. Glands on both sides of neck involved, axilla, and groin; spleen markedly enlarged; one of the tumours of the neck removed, and microscopical examination by Dr. James Ewing showed it to be Hodgkin's disease. Entire disappearance under six weeks' treatment with the toxins; no further treatment; regained normal weight; recurred about a year later: could not be persuaded to resume treatment. Died six months later.

(11) *Small Round-celled Sarcoma of Tonsil with extensive Metastases on both sides of Neck.*—Mr. C., aged 42. Marked loss of weight: referred to me May 29, 1906. Prognosis seemed so hopeless that no microscopical examination was made; toxins pushed as high as 20 mm. in pectoral region; severe reaction; continued to lose in weight under treatment. After thirty-one injections, advised to go home for a rest; tumours had slowly decreased in size under the treatment. After leaving the hospital he took a patent medicine of some sort; growth continued to decrease in size, and four months later had entirely disappeared. In June, 1907, a year later, he had a recurrence in the neck; exploratory operation; microscopical examination showed it to be round-celled sarcoma. Resumption of the toxins advised, but refused. Died of the recurrence within a year.

(12) *Round-celled Sarcoma of the Groin.*—E. C. B., male, aged 20. Operation performed at Springfield, Mass.; microscopical examination by Dr. J. J. Butler, pathologist to the hospital, showed it to be small round-celled sarcoma; recurred shortly after operation; disappearance under the toxin

treatment; recurrence in two months: again disappeared under renewed treatment. Well at present, one year later.

(13) *Sarcoma of the Neck; Round-celled Lymphosarcoma*.—E. L., male, aged 38. Referred by Dr. Stillman, of San Francisco, California; microscopical examination made by Drs. Ophyls, of San Francisco, and Welch, of Johns Hopkins; partial removal by operation; remaining tumour disappeared under the toxins: injections given for six months. Patient well at present, nine months.

(14) *Sarcoma of the Breast and Axilla*.—Mrs. J. G., in December, 1905, first noticed a small tumour in the lower axillary region on the left side; this slowly increased in size until March 23, 1906, when it was removed by operation. The report of the pathologist of the West Pennsylvania Hospital showed it to be a lymphosarcoma. The entire tumour was not removed at the time of the operation. The toxins were begun by myself, and then continued by the family physician for about three months. The patient has remained in perfect health since, upwards of three years.

(15) *Sarcoma of the Right Deltoid Region (Spindle-celled); well six years*.—H. B. M., male, aged 56. Removed by Dr. W. A. Brooks, of Boston, September, 1902; the tumour originated in the deltoid region. Examination, February, 1903, showed a small mass in the lower extremity of the cicatrix, apparently a recurrence of the growth. Pathological report by Dr. Wright, of the Massachusetts General Hospital Laboratory: spindle-celled sarcoma. The toxins were given by myself for two to three weeks, and then continued by the family physician for about three months. The patient is well at present, six years later.

(16) *Large, Recurrent Spindle-celled Sarcoma of Cheek*.—F. Q., male, aged 63, in January, 1904, noticed swelling in the middle of the right cheek: removed one week later; recurred almost immediately, and grew very fast. March 2, 1904, the patient came under my care: at this time there was a hard mass in the central portion of the right cheek, about 2 in. in diameter and $\frac{1}{2}$ in. thick. An attempt was made to remove the growth, but this was impossible without sacrificing almost entire cheek. Pathological examination showed the tumour to be spindle-celled sarcoma. Immediately after the wound had closed the patient was put upon the combined X-ray and mixed toxin treatment, which was continued for about three months, at the end of which time the growth had disappeared and the cheek was apparently normal. August 15, 1909, patient in perfect condition.

At a recent meeting of the Medical Society of Greater New York I showed eight patients who had been treated for inoperable sarcoma with the toxins, and in three of the eight the limbs—leg in two cases, and arm in the other—had been saved from amputation. Seven cases well from two to fourteen years, and the eighth is well over one year.

In the discussion of these cases certain criticism was offered by a surgeon which is typical of the sort of criticism the method received in former days, but which has become less and less frequent in recent years. No criticism was made as to the accuracy of the diagnosis in these cases, nor of the fact that the tumours disappeared and the patients themselves were in perfect health. The patients were present as visible proof of the latter fact, but this was the line of reasoning: (1) The treatment, if of the value claimed, should—after fifteen years—have become generally accepted all over the world and universally adopted. (2) The critic had just returned from Europe, and stated that the treatment was not generally used or accepted there: *ergo*, it could not be of value. Furthermore, the critic had himself tried it in a certain number of cases many years ago, and had not obtained the same results as myself.

I will leave the answering of such arguments to others with greater love for disputation than myself. I will only call attention to one fact, apparent to anyone familiar with the history of medical discoveries, and that is that the relative value of such discoveries bear not the slightest relation to the rapidity of their acceptance by the medical profession. Numerous examples will doubtless occur to you, but few more striking than the one cited by Dr. Eccles in his admirable address on "Darwinism and Malaria," *New York Medical Record*, January 16, 1909.

In conclusion I cannot do better than quote from a recent and unpublished paper of mine: "It is natural that any new method of treatment of disease should stand a certain definite test before it can hope to secure recognition. When it comes to the consideration of a new method of treatment for malignant tumours, we must not wonder that a profession with memories overburdened with a thousand and one much-vaunted remedies that have been tried and failed takes little interest in any new method and shows less inclination to examine into its merits. Cold indifference is all it can expect, and rightly too, until it has something beside novelty to offer in its favour. Sixteen years ago, when I began to use the toxins for inoperable sarcoma, I did not expect the profession to adopt the method. I was perfectly willing to wait until its great objection of novelty had given way to time, and my own results had been duplicated and confirmed by other observers. No one could see the results I saw and lose faith in the method. To see poor hopeless sufferers in the last stages of inoperable sarcoma show signs of improvement, to watch their tumours steadily disappear, and finally see

them restored to life and health, was sufficient to keep up my enthusiasm. That only a few instead of the majority showed such brilliant results did not cause me to abandon the method, but only stimulated me to more earnest search for further improvements in the method."

The results within the last two years, due to Dr. Tracy's improved method of preparing the toxins, have been decidedly superior to those obtained before. They now comprise fifty-two personal successes and at least twice that number in the hands of other men, which, I think, should be sufficient to convince the majority of the profession that the treatment of inoperable sarcoma by certain bacterial toxins contains a principle of sufficient value to be entitled to more careful consideration than it has yet received, and if I have succeeded in impressing the Fellows of the Royal Society of Medicine with the correctness of this view, I shall feel more than repaid for my visit to England.

In closing, I wish to state that the results that I have reported would never have been possible without the help of others, and I desire to again express my deep sense of obligation to Dr. B. H. Buxton, Professor of Experimental Pathology at Cornell University (Medical Department), for early and continual help in the preparation of the toxins. Whatever efficiency they have is largely due to his skill and patient co-operation. I desire also to acknowledge a great debt to the late Dr. William T. Bull for most generous help and encouragement, especially in the earlier experiments with the living cultures. The large amount of clinical material could not have been obtained without his influence and co-operation. My thanks are also due to Dr. Martha Tracy and Dr. S. P. Beebe (of the Huntington Cancer Research Fund) for suggesting valuable improvements in the technique of preparing the toxins within the last two years.

DISCUSSION.

The PRESIDENT (Mr. Warrington Haward) said the Society was much much indebted to Dr. Coley for his very interesting address. They admired his perseverance in the investigation and the use of the method of treatment which he had described. It had been said that there was not sufficient scientific basis for the treatment, but Dr. Coley had shown that he arrived at his method by carefully considered investigations, which it might be hoped that he would continue successfully to prosecute. Moreover, in the treatment of disease they had all used with advantage remedies of which they had been unable to give a scientific explanation, and had relied on clinical results to justify them in such

treatment. They might hope, therefore, that increased experience and careful records of Dr. Coley's method would enable them to judge more accurately of the appropriate dose of the fluid and the frequency of administration for each case; and in the meantime it seemed to him that what Dr. Coley told them was sufficient to encourage them to try his method in a disease such as sarcoma, many cases of which were so hopeless.

Mr. BUTLIN said: I came down expecting a discussion on the address, and nothing would have given me greater pleasure than to take part in it. Although Dr. Coley and I have never met, we are old friends, because we have corresponded regularly. He has been good enough to send me copies of his papers from time to time. He has not only done that, but he has also sent me material for use, the mixed bacilli of erysipelas and prodigiosus, and I have used it at different times. Of course, I cannot talk about his address, because that would open a discussion, and Dr. Coley would not have a proper opportunity for replying. But I should like to tell this assembly what I know of this treatment of Dr. Coley's. During the last twenty-five years I have been largely consulted on malignant disease, and I have seen many different kinds of so-called "cancer cures." These cures have all gone through the same kind of course. In the first stage the cure was to cure cancer; in the second stage, the cure was not to cure cancer, but it was to retard its progress and prevent recurrence; and the last and third stage of a cancer cure was the stage of oblivion. With the exception of Dr. Coley's method, scarce a single one has survived. Dr. Coley's fluid was introduced sixteen years ago or more. In the first instance, it was hoped that it would cure not only sarcoma but carcinoma. Then it was found to have no effect on carcinoma, but it was still hoped it would cure sarcoma. If not, it was hoped it would prevent recurrence and relieve pain. Later, it had nearly fallen into the stage of oblivion, for, in addition to the natural distrust which our profession have of any kind of new cure for cancer, a sub-committee consisting of some of the best surgeons in America, appointed by one of the great American medical societies, inquired into Dr. Coley's method, and came to the conclusion that the fluid was useless against malignant disease. That was enough to damp the ardour of anyone but Dr. Coley. He, however, had such full confidence in his treatment that he continued to use it and to recommend it, until he has succeeded in convincing not only America but this country that it deserves the closest attention, and that an extended trial should be given it. The further history of cases of sarcoma of the bones of the lower extremity, alone, is sufficient to convince me that Coley's fluid is a very potent medicine. I have, until now, looked on sarcoma of the femur (unless it be giant-celled) as an invariably fatal disease. But a number of cases of sarcoma of the femur are now reported as living some years after the treatment by Coley's fluid, either with or without operation. The difficulties in the way of adopting Coley's treatment are: The preparation of the material, the discomfort and malaise produced by the injections, and the rare occurrence of cases of sarcoma. On the first and second of these difficulties Dr. Coley has furnished implicit instructions, and these should be carefully studied by those who

would practise his method. On the third of them, I would say that sarcoma is rare in the practice of each individual hospital surgeon; so rare in private practice that, during the last seven years in which I have been consulted on malignant disease, I doubt if I have seen one case of sarcoma in each year. I have very great pleasure in proposing a hearty vote of thanks to Dr. Coley for his address, and for the devotion to his art which he has shown in travelling all this distance (from America) to deliver it. He has already made converts in this country to his views by his printed papers. His visit will strengthen the faith of those who mean to try his fluid. I only wish America could spare him to us for six months or a year, that he might himself superintend the treatment of a series of cases.

Sir A. E. WRIGHT, in seconding the vote of thanks, said that it had been inspiring to hear from Dr. Coley's own lips an account of the wonderful results he had achieved in the treatment of sarcoma; and he felt it a privilege to express on the part of the Society its debt of gratitude to Dr. Coley for his address. He was convinced that, whereas in the case of this method of treatment the results which have been achieved were known only indirectly on the testimony of witnesses, there was nothing which was to those who wished to arrive at a correct judgment so helpful as the actual seeing and hearing of the author. He felt sure that Dr. Coley had inspired everyone in his audience with the conviction of his veracity and with a conviction of the reality of his cures; and in listening to him everyone must have appreciated how severe must have been the strain undergone in contending with a reputedly hopeless disease, in employing a method which involves the infliction of severe local and constitutional suffering and possible risk to life, and in carrying on such work in the face of chilling scepticism. Dr. Coley was, he thought, entitled to receive their warmest congratulations and their tribute of admiration for the pluck and grit and doggedness which he had displayed in carrying his work through to results such as he had just recounted. There was, however, another aspect of Dr. Coley's work which ought, he thought, to be adverted to. Dr. Coley's method apparently rested on a purely empirical basis, and it was applied without any kind of scientific control. So distant, in fact, were the relations between this method and scientific thought that Dr. Coley's addresses had left his hearers in doubt as to whether he administers his bacterial filtrates with intent to produce a direct toxic and necrotic effect selectively upon the neoplastic cells, or whether he administers them as vaccines on the assumption that we have in sarcoma a concomitant streptococcic infection, or whether he employs them after the manner of a quack medicine without any thought of their mode of action. He confessed that he would have been grateful to have learned from Dr. Coley of some method of standardizing bacterial filtrates which are employed; he would have been glad to have learned why filtrates of prodigious and no others are added to his streptococcus filtrates; and, above all others, he would have been glad to have learned what changes are produced in the blood by successful inoculation in order that these might be employed in controlling and guiding the treatment. In all these hopes he had been disappointed. He

thought he could detect the same note of disappointment in Mr. Butlin's suggestion that steps should be taken to persuade America to lend Dr. Coley to England for a twelvemonth to take over the direction of his treatment in this country. Mr. Butlin was perhaps reflecting that in the absence of Dr. Coley we have no means of conducting his treatment aright. There here stood revealed, he took it, a great lacuna in Dr. Coley's work. Until that lacuna had been filled up by laboratory work done in conjunction with Dr. Coley's treatment, he was afraid it was impossible to feel any assurance that the results which had been achieved by Dr. Coley would be again realized here.

Dr. COLEY, in replying to the vote of thanks, said that he desired to express his deep appreciation of the interest shown and the gracious reception given his address by the members of the Society. He hoped the Society would permit him to say a word in reply to the proposer and seconder of the vote of thanks. In response to the remarks of Mr. Butlin, regarding the adverse report upon the value of the mixed toxins made by the Committee of the New York Surgical Society twelve years ago, he would say that that Committee was composed of three men. One of these, Dr. A. J. McCosh, had since been convinced of the value of the toxins, and had sent Dr. Coley a number of cases for treatment with the toxins during the last few years. The second member of that Committee was Dr. A. G. Gerster, and he had been convinced of the value of the toxins so thoroughly that he employs them at the Mount Sinai Hospital, not only in inoperable cases, but uses them after primary operations as a prophylactic against recurrence. Dr. Coley stated that, some four years ago, Dr. Gerster had sent him a patient with primary round-celled sarcoma of the tonsil, with extensive metastases in the neck. A partial operation had been performed, but the growth was too extensive for complete removal. The diagnosis had been confirmed by microscopical examination made at two laboratories. One large hospital had given him but a few weeks to live. The patient was admitted to the General Memorial Hospital in October, 1905, and under seven weeks' treatment with the mixed toxins the tumour entirely disappeared. Dr. Coley then read two letters from Dr. Gerster, one written directly after the tumours had disappeared, and the other after he had examined the patient and found him well, three years later. The letters were as follows :—

Copy, Letter No. 1.]

NEW YORK, *December 1, 1905.*

MY DEAR DR. COLEY,—It is my agreeable duty to congratulate you most sincerely on the brilliant achievement of the treatment you have given to our patient, Miller. Most certainly I have never seen anything like it. The tonsil looks now like a normal organ, and the large glandular and periglandular swelling of the neck has entirely disappeared. I hope it may turn out to be a permanent result. Thanking you for the interest taken in this seemingly hopeless case, I remain gratefully yours,

ARPAD G. GERSTER.

Letter No. 2.]

NEW YORK, June 17, 1908.

MY DEAR DR. COLEY.—Thank you for your note informing me about the brilliant and lasting result in the case of Harry Miller. It is the most gratifying case within my experience. May you have many more such! Truly yours,

A. G. GERSTER.

Dr. Coley further stated that he had shown this patient before the Society of Greater New York, in February, 1909, in perfect health, with no trace of the tumour either in the tonsil or neck. He added that the patient remained well at present. Dr. Coley stated that instead of in the beginning advising the mixed toxins as a method of treatment for cancer in general, he had begun by strictly limiting it to cases of inoperable sarcoma, and only after long experience had he felt justified on basis of the results obtained in extending its field of usefulness as a prophylactic after operation, and before operation to the limited group of cases where operation meant the sacrifice of a limb. With reference to the remarks of Sir Alnroth Wright, Dr. Coley stated that he must take exception to the method being classed as purely empirical and in the nature of a quack remedy, without laboratory basis. He had tried to show in his paper that the method was an absolutely scientific one: (1) Because it was founded upon a long array of demonstrable clinical facts—namely, a large series of cases of inoperable sarcoma that had disappeared under attacks of accidental erysipelas, and the patients had remained permanently cured. (2) The method rested upon the further fact that in a large number of cases of inoperable sarcomas treated with the mixed toxins of erysipelas and *Bacillus prodigiosus* the tumours had disappeared, and a goodly proportion of these cases had remained well from three to fifteen years, the diagnosis having been verified clinically and microscopically by the most competent men in surgery and pathology. (3) The addition of the *Bacillus prodigiosus* was not an empirical thing at all, but rested upon laboratory investigations of Roger, who found that the *Bacillus prodigiosus* grown together with the streptococcus of erysipelas greatly increased the virulence of the latter. It was this fact that led Dr. Coley to try the addition of the *Bacillus prodigiosus* to the erysipelas toxins. (4) The method during the last two years had been submitted to actual laboratory tests, and the investigations of Dr. Martha Tracy and Dr. S. P. Beebe, of the Huntington Cancer Research Fund, at the Loomis Laboratory, Cornell University Medical School, had demonstrated that multiple sarcomas in dogs disappear under injections of the mixed toxins, and, still more important, under the injections of the *Bacillus prodigiosus* alone.